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USSR WORK ON FUNCTIONING OF CHEMORECEPTORS IN TOXICOLOGICAL PROCESSES

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[Numbers in parentheses refer to appended bibliography.]

Lately Soviet pharmacologists and toxicologists have begun to pay great attention to the reflex mechanisms which are involved in toxicological processes. However, this approach will prove constructive only if it goes beyond mere declarations that the principle of nervism is valid. It is not enough to state that reflex mechanisms participate in the effects produced by chemical agents. It is essential to establish where these reflexes originate, how they are propagated, and what their physiological significance is.

It is certain that the reflexes which originate at the chemoreceptors, organs whose existence was predicted by I. P. Pavlov (1), are of the greatest significance.

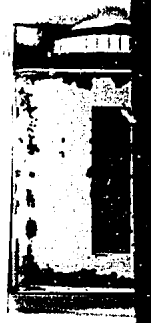
The nerve endings which possess specific chemical sensitivity, as predicted by I. P. Pavlov (1) and demonstrated by V. V. Zakusov (2) and V. N. Chernigovskiy (3), permeate all organs and all tissues of the organs. There can be no doubt, however, that the chemoreceptors of the carotid bulbs occupy an exceptional position as far as their sensitivity and response to the chemical changes which occur in the blood are concerned. These nerve formations must be regarded as watch-posts in the path of the blood stream within the brain.

This article deals with reflexes which originate at the carotid chemoreceptors when certain poisons have been resorbed and exert a so-called resorptive effect. There is every reason to believe that the regularities established in studying reflexes originating from the carotid bulbs may to some degree apply to other chemoreflexogenic zones.

It has been known for a long time that the principal and adequate stimulus inducing reflexes from the carotid bulbs is a shortage of oxygen in the blood. For that reason, the so-called anoxic poisons, i.e., poisons which inhibit tissue respiration, are strong stimulants of the carotid chemoreceptors. Cyanides and sulfides belong to this class of poisons. It is well known that the shortness of breath which is produced by these poisons and also the concomitant rise in blood pressure represent to a predominant extent a reflex from the carotid bulbs.

At present, several hypotheses are available which explain the reasons for the excitation of the carotid chemoreceptors that arises when there is a shortage of oxygen in the blood and whenever anoxic poisons act on these receptors.

According to the ideas of Winder (4) and of other American investigators, for instance Gesell and Hansen (5), the stimulus exerted on the carotid chemoreceptors is the result of the formation of acidic products which accumulate in the tissues in consequence of anoxia. On the other hand, the Swedish school of Professor Liljestrand holds that, as a result of anoxia, acetylcholine is formed in the tissue of the carotid bulbs, and that this acetylcholine is the immediate stimulant that produces impulses which are dispatched from the carotid bulbs to the nervous centers along Hering's nerve (the sinus nerve). (6)



A pharmacophysiological analysis of the sensitivity of the carotid receptors which has been carried out by our group demonstrated that neither of these hypotheses is valid.

A systematic and detailed investigation which has been conducted at our laboratory by M. L. Belen'kiy leads to the conclusion that the immediate cause of the excitation that originates at the chemoreceptors is a disturbance in them of the tissue energy balance, or more precisely, a prevalence of the scission of macroergic bonds over their resynthesis.(7) A disturbance of the energy balance of this type is produced by anoxemia and anoxic poisons. It can also be produced by some other chemical agents and influences, particularly the so-called Pasteur poisons.

The hypothesis advanced by Belen'kiy makes understandable the physiological significance and direction of the reflexes which originate when the chemoreceptors are excited as a result of anoxemia. If the immediate cause of the origination of impulses which brings about these reflexes is a disturbance of the energy balance in the tissue, then it is entirely natural to regard these reflexes as directed toward the restoration of the disturbed balance.

It is actually true that the stimulation of the respiration and the increase in the blood pressure, which are characteristic for reflexes originating in the carotid bulbs, are directed towards furnishing the tissues with a supply of oxygen, which is so necessary for raising the level of oxidative processes and restoring the energy balance of the tissues that has been disturbed.

Investigations undertaken by our workers demonstrated that the reflexes which are induced by the action of anoxic poisons, i.e., of cyanides and sulfides, do not influence the respiration and blood circulation only, but also have other effects. It is significant, however, that all reflexes, the existence of which has been established, have a distinct bearing on the restoration of the disturbed energy balance of the tissues.

The stimulation of the respiration and the increase in the minute [momentary?] volume of the heart have the effect of increasing the supply of oxygen available to the tissues, a condition which results in an increased intensity of the oxidation processes necessary for the restoration of the energy balance. The same purpose of supplying more oxygen is served by a speedy increase of the oxygen capacity of the blood and necessitates such an increase. This increase can be achieved by an augmentation of the number of erythrocytes. As has been shown in the experiments by Belen'kiy and Stroykov with cyanides (8) and by V. K. Zbruzhinskiy in experiments with hydrogen sulfide, reflexes which are transmitted to the spleen arise at the carotid chemoreceptors whenever these poisons act on them. As a result of the constriction of the spleen which takes place, an additional quantity of erythrocytosis is released into the circulating blood. In other words, a reflex erythrocytosis is established.

It is obvious that for the restoration of the energy balance, not only oxygen, but also an excess of nutrient material in the form of glucose must be present in the blood. A. A. Petropavlovskaya has actually shown that a reflex hyperglycemia is an obligatory reaction to the effect of cyanides. (9) Poisoning with hydrogen sulfide has the same effect, as has been shown recently by Zbruzhinskiy.

The medullar layer of the suprarenals is involved when this reflex originates at the carotid chemoreceptors: a reflex secretion of adrenalin serves as an intermediate link between the reflex and the development of hyperglycemia.

Increased secretion by the suprarenals as an intermediate reflex reaction caused by the excitation of the chemoreceptors has other effects besides the induction of hyperglycemia. Ye. S. Fedorchuk established that in the rise of blood pressure which is observed as a result of the action of poisons on the carotid chemoreceptors, hyperadrenalinemia induced by reflexes from the carotid bulbs also plays an important role. (10) If the suprarenals have been extirpated, the pressor reaction arising after the administration of poisons is much less intense than in animals whose suprarenals are intact.

The medullar layer of the suprarenals is not the only endocrine gland which is drawn into the general reaction of the organism whenever reflexes arise in response to the action of poisons on the carotid chemoreceptors.

The mobilization of the secretory activity of endocrine glands as organs which directly control tissue metabolism becomes completely understandable when the reflexes arising subsequently to the action of poisons on chemoreceptors are regarded as reactions directed towards the restoration of the energy balance of the tissues.

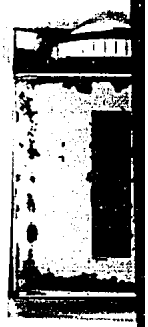
Investigations by A. A. Belous have demonstrated that whenever hydrocyanic acid and cyanides which have been resorbed exert an action on the carotid chemoreceptors, reflexes acting on the neurohypophysis arise. The antidiuretic effect which then results is produced by a reflex secretion of the antidiuretic hormone of the pituitary gland. (11)

It is highly probable that the reflex limitation of the elimination function of the kidneys subsequent to the action of anoxic poisons is one of the reactions that are directed towards the restoration of the disturbed tissue metabolism. One may also assume that among the regulating functions directed towards the restoration of the disturbed metabolism, there must be appropriate changes not only in the elimination function of the kidneys, but also changes in the functioning of the intestinal tract which assure that a supply of nutrient substances, forming a source of the energy needed by the body, is provided.

It has actually been found in Startsev's recent experiments that upon interaction of a solution of cyanide with the isolated carotid sinus there is a temporary stoppage of the peristalsis of the intestines, which, of course, makes certain that the contents of the intestine will be resorbed to a fuller extent.

Thus, a many-sided investigation of the reflexes originating at the carotid bulbs and taking place upon the action on these bulbs of anoxic poisons, i.e., poisons which suppress tissue respiration, such as cyanides and sulphides, indicates that these reflexes extend to the most diverse functions of the organism, and that all reflexes which arise in this connection can be regarded as directed towards the protection of the organisms from the consequences of tissue asphyhiation. In other words, these reflexes restore the tissue metabolism which has been interfered with by the poison. The question arises as to whether the regularities found by us in relation to anoxic poisons extend to other poisons which interfere with tissue metabolism. Another problem is whether the reflexes originating at the chemoreceptors, particularly the carotid chemoreceptors, participate in the general aspects of the action of these poisons.

It is obvious that the solution of these problems is of great significance for toxicology. They must first of all be considered with reference to poisons which bring about the hemic type of anoxemia, i.e., poisons which lower the oxygen capacity of the blood by reducing the quantity of free hemoglobin. One of the poisons of this type is carbon monoxide, which forms carboxyhemoglobin. Other poisons of this type are the numerous substances which bring about formation of methemoglobin.



It is known that in this form of anoxemia, notwithstanding the considerable reduction of the oxygen content in the blood, its tension in the plasma, i.e., the degree of saturation of the plasma with oxygen, does not change perceptibly. This circumstance makes many investigators doubt as to whether a reaction on the part of the chemoreceptors to a shortage of oxygen in the blood may take place in the hemic type of anoxemia. The majority of American investigators are of the opinion that the carotid chemoreceptors and other chemoreceptors may react only to changes in the level of the oxygen tension in the plasma, but not to a change in the quantity of oxygen in the erythrocytes, because the chemoreceptors are in contact with the blood plasma and do not come in touch with the erythrocytes or use the oxygen contained in them. On this ground, certain foreign scientists categorically deny that reflexes from the carotid bulbs may form one of the aspects of poisoning with carbon monoxide. (13, 14)

It must be said that the theoretical considerations on which this denial of the participation of reflexes from the carotid bulb is based are not very convincing, particularly if these reflexes are regarded as a result of changes in the tissue metabolism of the carotid bulbs themselves.

The tissue metabolism of the carotid bulbs must possess a great degree of intensity and for that reason react not only to the tension of the oxygen in the plasma, but also to the total quantity of oxygen which is present in the whole blood.

Of course, the problem in regard to the possible participation of reflexes originating at carotid bulbs in phenomena typical for the toxicology of carbon monoxide cannot be decided by abstract considerations, but must be solved experimentally. Experiments pertaining to this subject were conducted by M. A. Grebenkina. Her experiments demonstrated convincingly that at least in acute carbon monoxide poisoning, reflexes from the carotid bulbs participate and are of considerable significance.

It is worthy of attention that these reflexes are not limited to an excitation of the respiratory center but also exert an influence on the morphology of the blood and the chemical processes taking place in it, just as reflexes which originate under the action of anoxic poisons do. Grebenkina has shown that in cases when animals killed with carbon monoxide exhibit a strong erythrocytosis, this reaction has been produced by a reflex transmitted from the carotid bulbs to the spleen. This reaction is absent when the carotid bulbs have been treated with novocain or extirpated. It was found that the constrictions of the spleen are weaker in animals when the suprarenals have been removed from them. It is obvious that the secretion of adrenalin is an intermediary humoral link in this reflex reaction.

The same humoral link is active in hyperglycemia which is observed upon poisoning with carbon monoxide. Grebenkina has proven that this hyperglycemia is a reflex originating at the carotid bulbs and that it is not observed in animals with denervated carotid bulbs. At the same time, it has been shown that this reaction is absent after the suprarenals have been eliminated. It is obvious that in response to anoxemia produced by carbon monoxide a reflex originates in the carotid bulbs which induces hypersecretion of adrenalin, and that the hyperglycemia which develops thereupon involves a mobilization of the glycogen of the liver and a consequent increase in the level of the sugar in the blood. Thus, experimental results lead to the conclusion that the reflexes from carotid bulbs which are characteristic for anoxic poisons also arise in poisoning with substances which produce the hemic form of anoxemia. This applies to carbon monoxide poisoning as well as to intoxication with other agents which exert an anoxic activity.

There can be no doubt that reflexes of this type may originate as a result of the resorptive effect of many poisons, in view of the fact that the majority of toxic chemical agents exert a persistent toxic effect for the precise reason that they are capable of acting directly or indirectly on the tissue metabolism. Such reflexes must arise because acute changes in tissue metabolism inevitably act on the chemoreceptors. From our point of view, the chemoreceptors must be regarded as sentinels which protect tissue metabolism, and above all the energy metabolism of the tissues.

Of basic significance is the participation in these reflexes of the higher divisions of the cerebrum. This participation has been proven in work done by our collaborators.

It has been demonstrated in experiments carried out by Belous and Grebenkina that a conditioned reflex can be formed on the basis of reflexes induced by poisons which act on the carotid bulbs. (12) For instance, Grebenkina has obtained shortness of breath (panting) as a conditioned reflex based on the reflex excitation of the respiration brought about by cytisine. Belous has obtained a conditioned reflex hypersecretion of the neurohypophysis on the basis of the unconditional reflex brought about by hydrocyanic acid acting on the hypophysis by the way of the carotid bulbs. It is obvious that the reflexes originating at chemoreceptors are subjected to an unceasing control by the cerebral cortex.

As can be seen from the data cited, we are attempting to treat the reflexes which originate at chemoreceptors as compensatory reactions. However, it would be erroneous to overestimate the protective significance of these reflexes when they originate as a result of the action of poisons. Obviously the reflexes in question have developed as adaptive reactions which are released in response to the hypoxic type of oxygen shortage resulting because an inadequate quantity of oxygen is supplied to the organism. If this condition exists, all the reflexes which occur actually contribute to bringing the organism out of its pathological state.

In other forms of anoxemia and anoxia, particularly when the poisoning is produced by substances which penetrate into the body through the lungs, many of the reflexes that develop may harm rather than benefit the organism. Thus, shortness of breath and stimulation of the blood circulation in poisoning with gaseous anoxemic substances contribute to a higher degree of resorption of the poison by the tissues and render the poisoning more severe.

The violent activity which the chemoreceptors develop in acute poisonings cannot be regarded as a physiological reaction: it must be regarded as one of the exceptional reactions which I. P. Pavlov ascribed to extraordinary conditions typical for the pathological state.

Thus, we are justified in regarding these reactions as a part of the toxicological process induced by poisons.

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